REMARKS

Claims 35-62 are pending. Claims 35-37, 41-43, 48-52, and 54-62 are amended. The phrase "wherein at least one endogenous κ light chain locus of the transgenic mouse is not disrupted" added to claims 35 and 48 for clarity, is supported by the specification (See specification, for example, page 6, lines 16-17). No new matter has been added. The office action is discussed below.

Obviousness Rejections

On pages 3-11 of the Office Action, the Examiner has rejected claims 35-62 under 35 USC § 103(a) allegedly as being unpatentable over Kucherlapati patent in view of Mendez and Popov. Applicant respectfully traverses the rejections. In response applicant refers to the arguments and the declaration of Dr. Gonzalez Fernandez, submitted previously, and reiterate that the claimed inventions are not taught or suggested by the prior art.

Applicant notes that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43. Thus, the examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

It appears that the Examiner still believes that the ratio of human lambda to kappa light chains produced in the human lambda chain transgenic mouse was not "unexpected" and the Examiner further speculated "the skilled artisan reading Mendez would have had a reasonable expectation that introducing small human light chain YACs into mice would alter the kappa/lambda light chain ratio to a more human ratio." Applicant submits that the difference is attributable to the difference in genes involved and the authentic germline configuration (see specification, for example, pages 6-7, more specifically, page 6 lines 6-11), rather than just the YAC size or allele number per se. Regarding the Examiner's speculation that "Xenomouse I does indeed have a human kappa light chain loci and not a lambda locus as claimed, the fact that expression of human kappa in mice shifted the light chain ratio towards a human ratio", applicant points out that it is not only the lambda locus, - - rather the YAC according to the instant invention has an authentic germline configuration, which is different from that of Kucherlapati and Mendez (see specification, for example, pages 4, 6-7, 11-12, and claims 36-39). Moreover, the transgenic mice used by Kucherlapati and Mendez have disrupted endogenous Ig heavy and light chain loci. In contrast, the claimed invention discloses mice wherein "at least one endogenous κ light chain locus of the transgenic mouse is not disrupted" (See specification, for example, page 6, lines 16-17, and amended claims 35 and 48). Therefore, the alleged expectation provided by Kucherlapati or Mendez, and as speculated by the Examiner is irrelevant to the instant invention. Thus, combination of Kucherlapati and/or Mendez with the YAC of Popov can not provide any reasonable expectation of success of producing the "transgenic mice" according to the instant invention.

Applicant reiterates that the surprising results obtained with the present invention further establish patentability, and the examiner has not demonstrated anything to the contrary. *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); MPEP § 716.02(a). As explained by the Federal Circuit:

> [W]hen an applicant demonstrates *substantially* improved results ... and *states* that the results were *unexpected*, this should suffice to

establish unexpected results *in the absence of* evidence to the contrary.

In re Soni, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (emphasis in original).

Applicant submits that until the instant invention, there were no successful production or reporting of a "transgenic mouse" carrying human λ chain and expressing human λ chain locus equal or greater than the mouse endogenous κ chain locus (See specification, for example, page 3, lines 10-20).

Applicant also submits that both Kucherlapati and Mendez describe disruption of endogenous mouse Ig heavy and light (both κ and λ) chain loci to achieve the desired expression of introduced human Ig genes (See for example, Kucherlapati *et al.*, columns 11-12, more specifically, col. 11 lines 30-36; Mendez *et al.* pages 146, 148, 154-155). Applicant would like to inform the Examiner that Mendez used first generation Xenomouse, (as described in, Green *et al. Nature Genetics* 7: 13-21, 1994), which not only introduced human heavy chain and kappa light chain YACs but also contained two functionally inactivated mouse heavy and kappa light chain alleles (see Mendez *et al.*, page 146, right column and page 148, paragraph bridging left and right columns; also see for details, Green *et al.*, page 19, first column). Applicant also would like to inform the Examiner that the increased expression of human Ig heavy and light κ genes by the transgenic mouse (the Xenomouse) used by Mendez is attributed to the inactivation of the endogenous mouse Ig heavy and light κ (see Green *et al.*, page 19, first column, which describes: "confirming that inactivation of the mouse heavy and κ genes greatly increased levels of fully human antibodies"). Applicant points out that, instant invention does not require inactivation of mouse heavy and kappa light chain alleles nor does require disruption of endogenous mouse Ig heavy and light (both κ and λ) chain loci to achieve the desired expression of introduced human Ig genes. (See specification, for example, page 6, lines 16-17). In addition, the transgenic mouse according the invention show high expression and is able to compete with the endogenous mouse κ locus (see specification, for example, page 4, lines 8-9, and

claims 36). However, the transgenic mice containing YAC according to the invention also can express human Ig genes when the endogenous mouse Ig heavy and/or light (κ or λ) chain loci are disrupted (See specification, for example, page 6, lines 18-19). Therefore, it appears that the Examiner has incorrectly equated the present invention to the prior art disclosure.

Looking further into the Xenomouse I, when the yK1 comprising sequences from the human kappa light chain locus was transfected into normal mice (with endogenous kappa light chain loci not disrupted) only 5-9% of the $B220^{++}$ splenocytes expressed surface human kappa (see Green *et al.*, page 16, first column, and Figure 2b). This is contrary to the present invention, wherein mice containing the YAC are capable of expressing both human lambda and mouse kappa at a similar ratios (see specification, page 22 and Figures 3 and 4a). Therefore, due to unexpected properties of applicant's use of the YAC, the transgenic mice whose endogenous light chain genes had not been disrupted have $B220^{++}$ cells expressing 43% of the introduced human Ig lambda (see specification, page 22, line 11) in comparison to the yK1-containing transgenic mice disclosed in Green *et al.*, wherein only 5-9% of the $B220^{+}$ splenocytes expressed surface human kappa. This clearly shows that the transgenic mice produced according to the present invention are remarkably different than those in the prior art.

Moreover, the Xenomouse I required disruption of endogenous mouse heavy and kappa light chain loci, and introduction of YAC comprising sequences from both the human heavy chain locus and kappa light chain locus to achieve human-like ratios of kappa and lambda light chain genes to be expressed in the Xenomouse I. Therefore, it is not just the size of the YAC, but its properties as well. Contrary to the assertions of the Examiner, the expression ratios of kappa and lambda light chain genes in the transgenic mouse of the present application could not have been predicted from the prior art or the combination of the arts.

In order to expedite the prosecution, and without acquiescing to the propriety of the rejection of the claims 35-62, applicant amends claims 35 and 48 for clarity by adding the phrase "wherein at least one endogenous κ light chain locus of the

transgenic mouse is not disrupted." The amendment is supported by the specification (See specification, for example, page 4, lines 8-9 discloses "the translocus shows high expression, and is able to compete with the endogenous mouse κ locus"; page 6, lines 16-17, which discloses that "with similar efficiency as endogenous mouse κ and at the same time as or before the endogenous κ locus"; indicating that "the endogenous κ light chain is not disrupted"). Applicant also amend claims 35 and 48 for clarity by adding the phrase "a yeast artificial chromosome (YAC), wherein the YAC contains at least a majority of the human Ig Vλ genes of cluster A and all the human Ig Jλ- Cλ segments in germline configuration." The amendment is supported by the specification and the previously presented claim 37. Applicant further clarify that the YAC is the translocus in the transgenic mouse according to the invention.

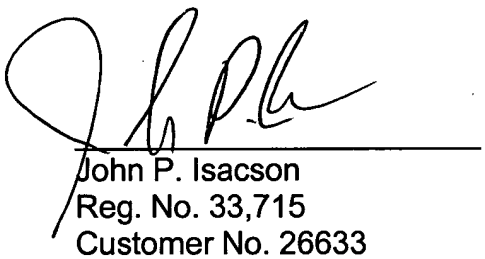
Amended claims 35 and 48 now recite that it is not necessary to disrupt (knock-out or silence or inactivate) the mouse endogenous κ light chain loci in order to achieve the stated and desired level of κ and λ light chains gene expression.

Therefore, applicant submits that the person having ordinary skill in the art would not consider the present invention obvious over the disclosures and combined teaching of Kucherlapati, Mendez and Popov. Accordingly, applicant respectfully requests withdrawal of the rejections.

REQUEST

Applicant submits that the claims 35-62 are in condition for allowance, and respectfully request favorable consideration to that effect. The Examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,



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